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Original Article

Efficacy of a combination of O-RADS, CEUS, and CA125, in identification of ovary-adnexal malignant lesions

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Abstract: Objectives: To evaluate the efficacy of a combination of Ovarian-Adnexal Reporting and Data System (O-RADS), contrast-enhanced ultrasound (CEUS), and cancer antigen 125 (CA125) in identifying malignant ovarian-adnexal lesions and improving diagnostic accuracy, providing a reliable reference for the evaluation and management of ovarian-adnexal malignancies to enhance patient prognosis. Methods: The study analyzed the diagnostic performance of O-RADS alone and in combination with CEUS and CA125 for distinguishing between benign and malignant ovarian-adnexal lesions. Sensitivity, specificity, accuracy, and Kappa values were calculated to assess the efficacy of these diagnostic approaches. Results: O-RADS alone showed a diagnostic sensitivity of 88.24%, specificity of 80.77%, and accuracy of 82.61% (Kappa = 0.719). When combined with CEUS, the diagnostic accuracy and Kappa value significantly improved. The combination of O-RADS, CEUS, and CA125 further enhanced the diagnostic performance, achieving sensitivity, specificity, and accuracy of 82.35%, 98.08%, and 94.20%, respectively (Kappa = 0.804). Conclusions: The combination of O-RADS, CEUS, and CA125 significantly improves the diagnostic accuracy of ovarian-adnexal malignant lesions, providing new clinical references for the evaluation and management of ovarian-adnexal malignancies and contributing to better patient prognosis.

Keywords: Ovarian-Adnexal Reporting and Data System, contrast-enhanced ultrasound, cancer antigen 125, ovary-adnexal, malignant lesions, diagnosis

Introduction

The ovary-adnexal region is a critical part of the female reproductive system, responsible for producing and releasing eggs as well as secreting estrogen and progesterone [1]. Among women, ovarian-adnexal malignancies are the second most common cancer after breast cancer, with late-stage mortality rates reaching 60% to 80%, making it the deadliest tumor among female cancers [2]. Early and accurate identification of malignant lesions in adnexal masses is essential for improving patient outcomes. However, current diagnostic methods have notable limitations.

Traditional tumor markers, such as cancer antigen 125 (CA125), exhibit high sensitivity for detecting malignancies but suffer from low specificity. For instance, inflammatory responses can also induce abnormal CA125 expression, reducing its utility for early screening of ovarian-adnexal malignancies [3]. Imaging-based diagnostic tools, such as the Gynecologic Imaging Reporting and Data System (GI-RADS), are widely used but lack global standardization, making their interpretation highly subjective and increasing the risk of misdiagnosis and missed diagnoses [4]. The International Ovarian Tumor Analysis (IOTA) proposed diagnostic criteria for ovarian-adnexal malignancies [5], but these criteria are reportedly unable to diagnose 20% to 24% of cases, requiring additional tests for comprehensive evaluation, which limits their convenience in clinical practice [6].

To address these challenges, the American College of Radiology released the Ovarian-Adnexal Reporting and Data System (O-RADS) ultrasound risk stratification guidelines in 2020 [7]. O-RADS provides a standardized interpretation of ultrasound reports and management recommendations for various risk categories, helping to reduce inconsistencies in the assess-

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ment of ovarian-adnexal lesions [8]. Numerous studies have validated the clinical utility of O-RADS in improving diagnostic accuracy for ovarian-adnexal malignancies [9, 10]. A recent expert review in the American Journal of Radiology highlighted O-RADS' potential as a future guideline for ovarian-adnexal diagnosis [11]. However, certain studies indicate that O-RADS' accuracy is compromised when patients exhibit similar symptoms across different diseases [12]. Addressing this limitation is key to optimizing O-RADS' clinical application.

To improve the diagnostic accuracy of O-RADS, researchers have explored combining it with other diagnostic methods. For example, Wang et al. analyzed the value of O-RADS combined with CA125 in diagnosing ovarian cancer [13], and Ruan et al. studied O-RADS with microblood flow imaging (MV-Flow) [14]. However, the use of CEUS in conjunction with O-RADS remains underexplored. CEUS, which provides detailed visualization of tissue micro-blood flow perfusion, is widely used for early assessment of various organ lesions [15]. It has unique advantages in diagnosing vascular and neurological lesions [16], but its standalone performance in ovarian-adnexal malignancy diagnosis has not shown significant superiority [17]. Nevertheless, we hypothesize that CEUS could complement O-RADS by addressing its limitations in differentiating diseases with overlapping symptoms, thereby enhancing diagnostic efficiency. Currently, no clinical studies have investigated this combination.

This study evaluates the combined diagnostic performance of O-RADS and CEUS in differentiating benign and malignant ovarian-adnexal lesions. To further enhance diagnostic accuracy, the tumor marker CA125 was incorporated as an additional observation. These findings aim to provide new insights and guidelines for diagnosing ovarian-adnexal malignancies, ultimately improving patient outcomes.

Materials and methods

Study design and patients

Patients suspected of having adnexal masses admitted to Henan Provincial People's Hospital from November 2021 to September 2024 were selected for retrospective analysis. The required sample size was calculated using PASS software, which indicated a minimum of 61 participants. After applying inclusion and exclusion criteria, 69 patients were enrolled.

Inclusion criteria: (1) Routine transabdominal or transvaginal ultrasonography indicated possible ovarian-adnexal lesions, and CEUS was performed. (2) Surgical or puncture biopsy histopathology was completed within three months of the CEUS examination. (3) Complete clinical data were available. (4) Age >18 years.

Exclusion criteria: (1): Missing or unclear ultrasound images. (2) CEUS failed to show both the lesion and the normal uterine myometrium. (3) Patients with multiple tumors. (4) Allergy to contrast media or other known allergies.

Among the included participants, 17 patients were diagnosed with ovarian-adnexal malignant lesions through pathological biopsy, while 52 were found to have benign ovarian-adnexal masses. This study was approved by the Ethics Committee of Henan Provincial People's Hospital [(2021) Ethical Review No. (214)]. The main flow of the study is illustrated in **Figure 1**.

Data extraction

CA125 Measurement: A 2 mL sample of fasting elbow venous blood was collected at admission using a procoagulant tube. After resting at room temperature for 30 minutes, the serum was separated by centrifugation at 3000 rpm for 10 minutes. CA125 levels were measured using a fully automated chemiluminescence analyzer (Roche e6000).

Two-Dimensional (2D) Ultrasonography: Transvaginal ultrasonography was performed in patients with a history of sexual intercourse. Patients were instructed to empty their bladders and adopt the lithotomy position during the examination. The ovarian borders, morphology, and internal echogenicity were carefully observed using the probe. For patients without a history of sexual intercourse, the bladder was filled by instructing them to drink water before the examination, and the examination was performed in the supine position.

Color Doppler Examination: The color Doppler flow imaging system was adjusted to its most sensitive settings to visualize the blood flow distribution in the ovarian-adnexal lesion. The

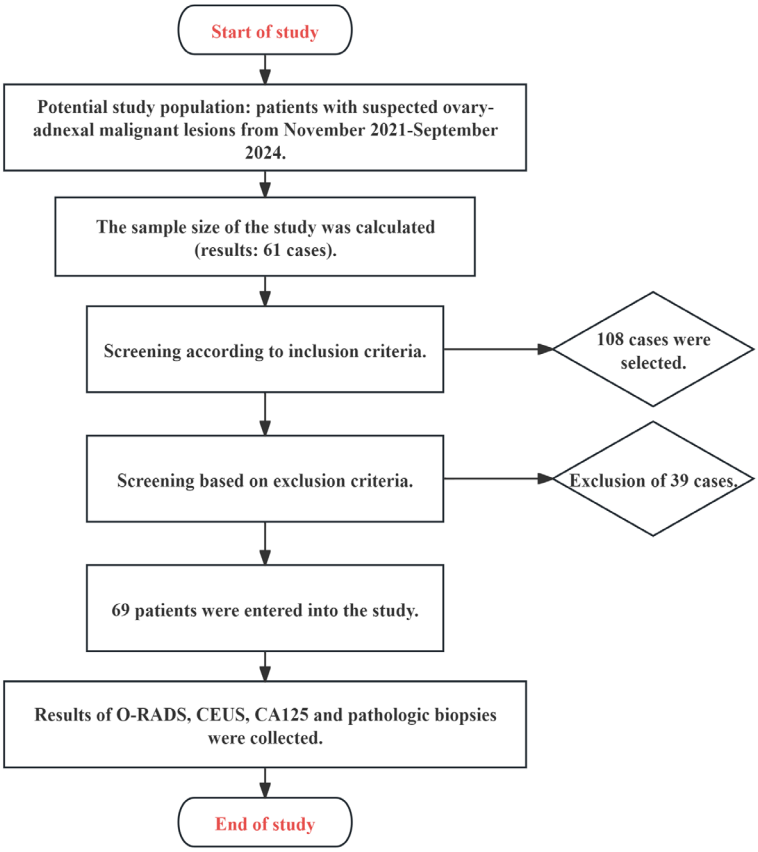

Figure 1. Flowchart of this work.

sampling frame was positioned at the area with the most abundant blood flow signals. Three or more consecutive spectral waveforms were obtained, and the resistance index (RI) and pulsatility index (PI) were measured to calculate their average values.

CEUS and Image Analysis: A 2.4 mL bolus of microbubble suspension was injected into the anterior elbow vein, followed by a 5 mL saline flush within 2 seconds. The contrast observation began immediately after the injection, focusing on the early and late enhancement intensity, shape, boundary, and presence of spillage in the lesion area. The full lesion needed to be contrasted with the myometrium. Ultrasonography quantitative TIC analysis software was used to automatically trace time-intensity curves. The lesion area was sampled manually, and the myometrium served as the control. The ultrasonography device used was a Philips Epiq Elite W equipped with an abdominal probe (C5-1) and an intracavitary probe (C10-3v). The contrast agent was sulfur hexafluoride microbubbles (SonoVue, 59 mg), and acoustic quantitative time-intensity analysis software was used for curve tracing.

O-RADS and CEUS result determination

Ovarian-adnexal lesions were classified using the O-RADS criteria and reviewed with CEUS by a senior sonographer. A secondary evaluation was performed by another physician of equivalent seniority, with both evaluators blinded to the pathological results. If the two physicians' evaluations were consistent, the result was recorded. In cases of discrepancy, a third senior ultrasound physician was consulted to finalize the evaluation. The O-RADS classification criteria are shown in **Table 1**. The O-RADS≥4 was (+).

CEUS Evaluation Criteria [18]: (1) The lesion exhibits an enhancement level higher than that of the uterine myometrium (high enhancement). (2) The contrast agent appears in the tumor earlier than in the uterine myometrium (early enhancement). (3) The distribution of the contrast agent within the tumor is uneven.

Diagnostic efficiency evaluation

Pathological biopsy served as the gold standard for diagnosis. Diagnostic outcomes were classified as follows:

True positive (a): Both the gold standard and the diagnostic scheme indicate malignancy (+). True negative (b): Both the gold standard and the diagnostic scheme indicate benignity (-). False positive (c): The gold standard indicates benignity (-), but the diagnostic scheme indicates malignancy (+). False negative (d): The gold standard indicates malignancy (+), but the diagnostic scheme indicates benignity (-).

The following formulas were used to evaluate diagnostic performance: Sensitivity = a/(a + d) × 100%, specificity = b/(b + c) × 100%, and

Table 1. Criteria for O-RADS classification

O-RADS classification	Level of risk	Detailed description
0	Unable to evaluate	Not applicable
1	Normal	Simple follicle ≤3 cm, corpus luteum ≤3 cm
2	Benign lesions (<1% risk of malignancy)	(1) Simple cyst (<10 cm) (2) Non-simple unilocular cysts with smooth walls (<10 cm) (3) Typical benign lesions (<10 cm): hemorrhagic cysts, mature teratomas, and endometriotic cysts, as well as para-adnexal cysts, peritoneal inclusion cysts, and hydrosalpinx
3	Low risk malignant lesions (malignant risk 1% - <10%)	(1) Simple or non-simple unilocular cysts ≥10 cm in diameter (2) Typical benign lesions ≥10 cm in diameter (3) Unilocular cyst with irregular cystic lining <3 mm in height (4) Multilocular cyst <10 cm with smooth inner wall, CS: 1-3 points (5) Solid component with regular borders, CS: 1 point
4	Intermediate risk malignant lesions (malignant risk 10% - <50%)	(1) Multilocular cyst without solid component: >10 cm, smooth cystic lining, CS: 1-3 points. Any size, smooth cyst lining, CS: 4 points; any size, irregular cyst lining and/or incomplete separation (2) Unilocular cyst with solid component, 0-3 papillae (3) Multilocular cyst with solid component, CS: 1-2 points (4) Solid component with regular borders, CS: 2-3 points
5	Malignant high-risk lesions (malignant risk ≥50%)	(1) Unilocular cyst with ≥4 papillae (2) Multilocular cyst with solid component, CS: 3-4 points (3) Solid component with regular borders, CS: 4 points (4) Irregular solid component (5) Abdominal fluid or peritoneal nodules

Note: O-RADS, Ovarian-Adnexal Reporting and Data System.

accuracy = (a + b)/total number of people × 100%.

Combined diagnosis: (1) O-RADS + CEUS: Malignancy was marked as (+) if both methods indicated malignancy. Benignity was marked as (-) if both methods indicated benignity, or if only one method indicated malignancy. (2) O-RADS/CEUS + CA125: Malignancy was marked as (+) if O-RADS (or CEUS) indicated malignancy and CA125 ≥35 U/mL (clinical reference value [19]). Benignity was marked as (-) if both methods or only one method indicated malignancy. (3) O-RADS + CEUS + CA125: Malignancy was marked as (+) only if O-RADS and CEUS indicated malignancy, and CA125 ≥35 U/mL. All other cases were marked as (-).

Outcome measures

Primary outcomes: Diagnostic accuracy of O-RADS combined with CEUS and CA125 for identifying benign and malignant ovarian-adnexal lesions.

Secondary outcomes: (1) Diagnostic accuracy of O-RADS alone in differentiating benign and malignant ovarian-adnexal lesions. (2) Diagnostic accuracy of CEUS alone in differentiating benign and malignant ovarian-adnexal lesions. (3) Diagnostic accuracy of O-RADS combined with CEUS in differentiating benign and malignant ovarian-adnexal lesions.

Statistical analysis

Data were analyzed using SPSS 24.0. Count data were expressed as [n (%)]. Comparisons between groups were performed using the chi - square test and Yates' Continuity Correction. Normality of continuous Data was assessed using the Shapiro-Wilk test. Normally distributed data were reported as ($\bar{x} \pm s$), and comparisons between groups were performed using the independent sample t-test. Non-normally distributed data were expressed as [median (interquartile range)], and the Mann-Whitney U test was used for intergroup comparisons. Logistic regression was used to analyze factors affecting diagnostic outcomes. Spearman's correlation coefficient was used to analyze relationships between variables. The Kappa test was used to evaluate diagnostic agreement. A higher Kappa value indicates greater diagnostic reliability. A *P*-value <0.05 was considered statistically significant.

Results

Pathological examination results

Pathological examination revealed that among the 52 patients with benign ovarian-adnexal masses, the common diagnoses were cystadenoma, endometriotic cyst, ovarian thecoma-fibroma, etc. Among the 17 patients with malignant ovarian-adnexal lesions, diagnoses included endometrioid adenocarcinoma and serous carcinoma, etc. Detailed baseline characteristics of the patients are presented in **Table 2**, while **Figure 2** illustrates typical imaging findings of a benign ovarian-adnexal lesion and a malignant lesion.

To further enhance the reliability of our findings, we analyzed factors potentially associated with ovarian-adnexal malignancies.

The analysis showed no statistically significant relationship between these factors and the presence of ovarian-adnexal malignant lesions (P>0.05, **Tables 3** and **4**).

Differentiating effect of O-RADS and CEUS on ovary-adnexal malignant lesions

First, the diagnostic performance of O-RADS alone for identifying ovarian-adnexal malignant lesions was analyzed. Among the cases assessed using O-RADS, 25 lesions were classified as malignant, with 15 true-positive cases confirmed by pathological biopsy. Of the 44 lesions classified as benign, 42 were true-negative. Compared with pathological biopsy, the sensitivity, specificity, and accuracy of O-RADS for diagnosing malignant lesions were 88.24%, 80.77%, and 82.61%, respectively (Kappa = 0.719).

Next, the diagnostic performance of CEUS alone was evaluated. CEUS detected 26 malignant lesions, including 15 true-positive cases confirmed by pathological biopsy. The sensitivity, specificity, and accuracy of CEUS for diagnosing malignant lesions were 88.24%, 78.85%, and 81.16%, respectively, with a Kappa value of 0.709, which was slightly lower than the Kappa value for O-RADS.

When O-RADS and CEUS were combined, the diagnostic results improved significantly. The combined method identified 51 benign lesions, including 48 true-negative cases, and 18 malig-

Table 2. Baseline information of patients

	Ovary-adnexal benign masses (n = 52)	Ovary-adnexal malignant lesions (n = 17)	t (or χ^2)	P
Age	54.85±8.26	56.65±6.87	0.811	0.421
Family history of disease			0.026	0.873
Have	8 (15.38)	3 (17.65)		
None	44 (84.62)	14 (82.35)		
Previous gynecological history			0.045	0.832
Yes	9 (17.31)	4 (23.53)		
No	43 (82.69)	13 (76.47)		
Weight (kg)	54.77±4.85	53.94±5.61	0.588	0.558
Diastolic blood pressure (mmHg)	75.87±4.90	76.65±6.48	0.526	0.601
Systolic blood pressure (mmHg)	104.56±8.27	106.59±7.53	0.898	0.373
Smoking			0.161	0.689
Yes	8 (15.38)	4 (23.53)		
No	44 (84.62)	13 (76.47)		
Pathological findings			-	-
Serous/mucinous carcinoma	-	10 (58.82)		
Adenocarcinoma	-	4 (23.53)		
Other	-	3 (17.65)		

nant lesions, including 14 true-positive cases. Compared with pathological biopsy, the combined diagnostic sensitivity, specificity, and accuracy were 82.35%, 92.31%, and 89.86%, respectively, with a higher Kappa value of 0.756, indicating excellent diagnostic consistency and clinical reference value (**Table 5**).

Differentiating effect of O-RADS, CEUS combined with CA125 on ovary-adnexal malignant lesions

We further analyzed the diagnostic efficacy of O-RADS and CEUS combined with CA125 for ovarian-adnexal malignant lesions. The results showed that combining CA125 with either O-RADS or CEUS improved diagnostic consistency, as reflected by the Kappa values (O-RADS+CA125: 0.727; CEUS+CA125: 0.738). However, these values were lower than the Kappa value observed for the combination of O-RADS and CEUS.

Notably, the combined use of O-RADS, CEUS, and CA125 achieved diagnostic sensitivity, specificity, and accuracy of 82.35%, 98.08%, and 94.20%, respectively, with a Kappa value of 0.804 - the highest Kappa value in this study (**Table 6**). Spearman's correlation coefficient analysis further revealed a significant positive correlation between the O-RADS grade and CA125 levels ($r = 0.520$, $P<0.001$), indicating that higher O-RADS grades were associated with higher CA125 levels.

To validate these findings, we plotted receiver operating characteristic (ROC) curves. The results showed that the diagnostic curve for the combination of O-RADS, CEUS, and CA125 had an area under the curve (AUC) of 0.929 ($P<0.05$), demonstrating excellent diagnostic performance (**Figure 3**).

Discussion

The incidence of ovarian-adnexal malignant lesions has been increasing in recent years. Due to their insidious onset and the lack of specific early clinical symptoms, most patients are diagnosed at advanced stages, leading to poor prognoses and high mortality rates [20]. Early diagnosis and treatment of ovarian-adnexal malignant lesions are critical to improving survival rates.

Ultrasonography remains the most commonly used screening method for ovarian-adnexal lesions. However, due to tumor characteristics such as "different manifestations of the same disease" and "same manifestations of different diseases", as well as variability caused by subjective factors among physicians, diagnostic

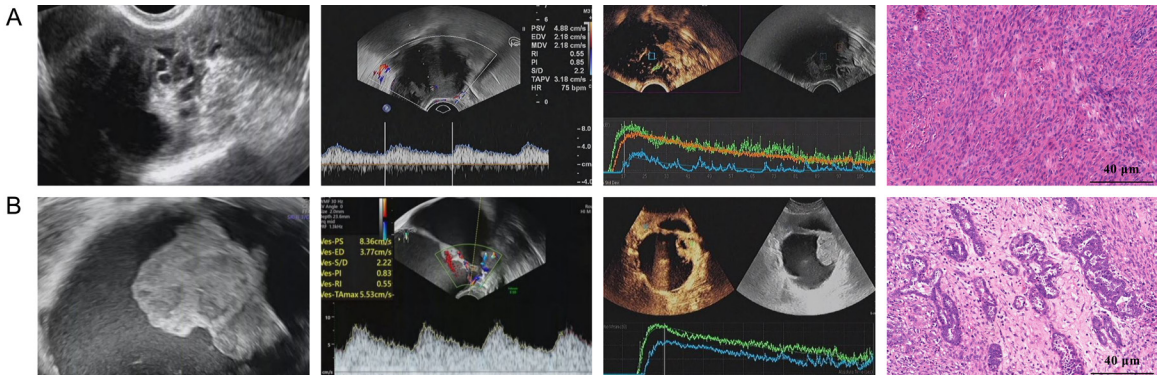

Figure 2. A: 32 years old, benign lesions, ovarian thecoma-fibroma. B: 45 years old, malignant lesions, endometrioid adenocarcinoma.

Table 3. Table of assignments

Variables	Assigned values
Malignant lesions	Benign = 1, malignant = 2
Family history of disease	No = 1, yes = 2
History of gynecological problems	No = 1, yes = 2
Smoking status	Non-smoker = 1, smoker = 2

accuracy can vary significantly [21]. Therefore, developing methods for early and accurate diagnosis of ovarian-adnexal malignant lesions has long been a challenge in gynecological ultrasound research.

In this study, we analyzed the diagnostic performance of O-RADS combined with CEUS for ovarian-adnexal malignant lesions, providing a valuable reference for future clinical practice.

The diagnostic performance of O-RADS alone in 69 patients showed a sensitivity of 88.24%, specificity of 80.77%, and accuracy of 82.61% (Kappa = 0.719). These results are consistent with previous studies on O-RADS. For example, Lu B et al. reported an accuracy of 87.5% for O-RADS in differentiating ovarian-adnexal malignant lesions [22]. However, since O-RADS is based on conventional 2D ultrasound, it struggles to differentiate quasi-solid from solid components and to visualize tissue microcirculation perfusion [23]. This limitation may explain the residual errors in diagnosing ovarian-adnexal malignant lesions using O-RADS alone.

Additionally, Assouline et al. highlighted that analyzing cystic components could improve the diagnostic performance of O-RADS for adnexal cystic masses [24], further emphasizing that O-RADS alone has limitations in clinical practice. These findings align with the general consensus that the diagnostic accuracy of O-RADS alone remains suboptimal.

In contrast, the diagnostic sensitivity, specificity, and accuracy of CEUS alone for ovarian-adnexal malignant lesions were 88.24%, 78.85%, and 81.16%, respectively, with a Kappa value of 0.709. Although its Kappa value was lower than that of O-RADS, CEUS still holds clinical reference value. With the rapid advancements in CEUS technology, this technique has demonstrated advantages in detecting small lesions and clarifying lesion borders [25].

By injecting a microbubble contrast agent through a peripheral vein, CEUS enhances the echo difference between blood flow and surrounding tissues via principles such as enhanced backscatter and altered acoustic attenuation [26]. This allows CEUS to accurately observe blood flow perfusion, direction, and vascularity within and around the lesion. It can even visualize small blood vessels (caliber <200 μm) and detect low-velocity blood flow (0.1-10 mm/s) in microvessels, overcoming the limitations of conventional ultrasound. Consequently, CEUS can display the vascular distribution and micro-perfusion within a mass, improving the accuracy of ultrasound in differentiating between benign and malignant lesions.

The infiltrative growth of malignant lesions depends on the presence of neoplastic and abundant blood vessels, as well as pathological fea-

Table 4. Multifactorial analysis affecting ovary-adnexal malignant lesions

Factors	B	S.E.	Wals	P	OR	95% CI
Age	0.028	0.037	0.572	0.449	1.028	0.957-1.106
Family history of disease	0.121	0.824	0.022	0.883	1.129	0.224-5.677
Previous gynecological history	0.396	0.779	0.259	0.611	1.486	0.323-6.846
Weight	-0.011	0.061	0.030	0.863	0.989	0.878-1.115
Diastolic blood pressure	0.027	0.057	0.228	0.633	1.028	0.919-1.150
Systolic blood pressure	0.034	0.038	0.828	0.363	1.035	0.961-1.114
Smoking	0.401	0.757	0.281	0.595	1.494	0.339-6.582

Note: B, regression coefficient; S.E., standard error; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5. Differentiating effect of O-RADS and CEUS on ovary-adnexal malignant lesions

		Pathological biopsy		Total	Kappa	Sensitivity	Specificity	Accuracy
		(+)	(-)					
O-RADS	(+)	15	10	25	0.719	88.24	80.77	82.61
	(-)	2	42	44				
CEUS	(+)	15	11	26	0.709	88.24	78.85	81.16
	(-)	2	41	43				
O-RADS+CEUS	(+)	14	4	18	0.756	82.35	92.31	89.86
	(-)	3	48	51				
Total		17	52					

Note: O-RADS, ovarian reporting and data system; CEUS, contrast-enhanced ultrasound.

Table 6. Differentiating effect of O-RADS, CEUS combined with CA125 on ovary-adnexal malignant lesions

		Pathological biopsy		Total	Kappa	Sensitivity	Specificity	Accuracy
		(+)	(-)					
O-RADS+CA125	(+)	14	7	21	0.727	82.35	86.54	85.51
	(-)	3	45	48				
CEUS+CA125	(+)	15	8	23	0.738	88.24	84.62	85.51
	(-)	2	44	46				
O-RADS+CEUS+CA125	(+)	14	1	15	0.804	82.35	98.08	94.20
	(-)	3	51	54				
Total		17	52					

Note: O-RADS, ovarian reporting and data system; CEUS, contrast-enhanced ultrasound; CA125, cancer antigen 125.

tures such as arteriovenous fistulae caused by tumor erosion. With increasing tumor aggressiveness, particularly in ovarian cancer, the internal blood supply becomes more abundant [27]. CEUS, with its ability to assess internal blood perfusion, provides a rapid and accurate clinical evaluation of ovarian-adnexal malignant lesions.

However, due to the variability in lesion pathology and the complexity of sonographic features, CEUS may lead to misdiagnosis or missed diagnoses in cases of atypical or overlapping contrast perfusion patterns. Additionally, challenges arise with "different images for the same disease" or "different diseases for the same image". Inexperienced ultrasonographers may further contribute to diagnostic errors [28]. These limitations explain why the Kappa value for CEUS is lower than that for O-RADS.

A study by Wang R et al. also demonstrated that diagnosing ovarian epithelial tumors based solely on CEUS is insufficient and that CEUS

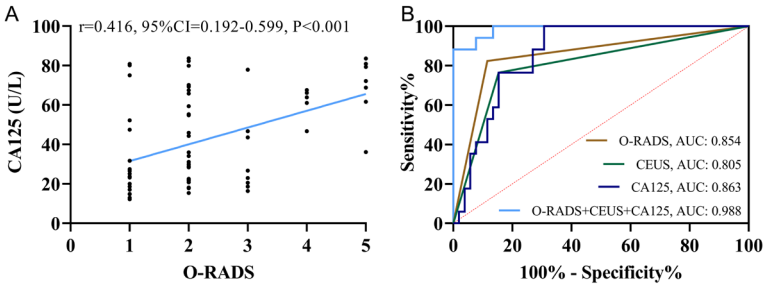

Figure 3. A: Correlation between O-RADS and CA125. B: ROC curves of O-RADS, CEUS, and CA125 for diagnosis of ovary-adnexal malignant lesions. Note: ROC, Receiver operating characteristic; AUC, area under curve.

should be combined with 2D ultrasound for improved diagnostic efficacy [29]. This conclusion aligns with our findings.

Compared with pathological biopsy results, the combination of O-RADS and CEUS significantly improved the accuracy of differentiating ovarian-adnexal malignant lesions, demonstrating its greater clinical utility (sensitivity = 82.35%, specificity = 92.31%, accuracy = 89.86%, Kappa = 0.756). The following reasons may explain these findings:

Although the O-RADS classification system has high diagnostic efficiency for ovarian-adnexal malignant lesions, its ability to detect blood flow in solid components of category 3 tumors and papillary structures in some cystic masses is limited. This can affect the grading of blood flow within the masses, thereby interfering with O-RADS classification accuracy [30].

Ultrasound contrast agents used in CEUS have unique molecular properties that allow for the detailed visualization of blood flow microcirculation within tumors. CEUS can accurately assess the enhancement time, intensity, and patterns of contrast agents in lesions [24]. It is particularly sensitive to microcirculatory and low-velocity blood flow perfusion, enabling the evaluation of lesion vascularity and the presence of solid components [31]. These capabilities compensate for the limitations of O-RADS, thereby enhancing its ability to differentiate ovarian-adnexal malignant lesions.

In contrast, for benign lesions, the use of CEUS does not significantly enhance O-RADS diagnostic performance, as benign masses typically lack solid components and have little or no blood supply. However, Hu et al. reported that CEUS demonstrates excellent diagnostic efficiency even for ovarian-adnexal benign lesions [32]. The discrepancy between their findings and those of this study may stem from differences in the CEUS evaluation methods and indicators used. In Hu et al.'s study, CEUS assessments included time-intensity curve analysis and quantitative evaluations, which offer more intuitive and accurate assessments of vascular perfusion patterns compared to qualitative observation methods [32]. Additionally, enhancement speed was included as an indicator in their study, alongside enhancement time, intensity, and patterns.

Furthermore, due to the diverse pathological types of ovarian-adnexal malignant lesions, there is significant variability in their ultrasound imaging characteristics. For certain rare types of malignant lesions, misdiagnosis or missed diagnoses may still occur even when CEUS is used in combination with O-RADS. To address these challenges, future research will focus on including a larger cohort of clinical cases to further validate and analyze these findings.

CA125 is a key tumor marker used in the clinical evaluation of gynecologic tumors, and its diagnostic sensitivity is well established. However, increasing evidence indicates that various conditions, such as inflammatory lesions and nerve injury, may cause abnormal elevations of CA125 [33, 34]. As a result, its specificity and accuracy in tumor identification have declined, including for ovarian-adnexal malignant lesions. Despite these limitations, the high sensitivity of CA125 for tumor detection remains invaluable.

In this study, we found that combining CA125 with imaging modalities significantly improved diagnostic performance for ovarian-adnexal malignant lesions. Specifically, the diagnostic Kappa values for O-RADS + CA125 and CEUS + CA125 were 0.727 and 0.738, respectively, compared to imaging alone. This highlights the ability of CA125 to enhance the diagnostic efficacy of O-RADS and CEUS. Supporting this finding, Zhang et al. reported that CA125 improves the accuracy of early breast cancer diagnosis [35], which aligns with our results.

Additionally, we observed that the combined use of O-RADS, CEUS, and CA125 achieved the highest diagnostic performance in this study, with a sensitivity of 82.35%, specificity of 98.08%, accuracy of 94.20%, and a Kappa value of 0.804. These results underscore the clinical value of this combined diagnostic approach. We attribute this success to the complementary roles of the three modalities: CA125 provides high sensitivity for initial screening, while CEUS and O-RADS serve as secondary validation tools, producing results highly consistent with pathological findings.

The ROC curve further confirmed the superior diagnostic performance of O-RADS + CEUS + CA125, with the highest AUC for identifying ovarian-adnexal malignant lesions. This evidence strongly suggests that this combined diagnostic approach will become a highly effective and clinically applicable scheme for differentiating benign and malignant ovarian-adnexal lesions in the future. Similarly, Haj-Mirzaian et al. demonstrated that combining traditional tumor markers with imaging significantly improves the diagnosis of malignant liver tumors [36], which is consistent with our findings.

Collectively, these results provide a rapid, accurate, and safe diagnostic protocol for evaluating benign and malignant ovarian-adnexal lesions, thereby offering a reliable prognosis and improving patient outcomes.

This study still has several limitations that should be addressed in future research. First, it was a single-center retrospective analysis with a relatively small size, which may lead to the randomness and bias into the statistical analysis. Second, the short follow-up may have affected the accuracy of analyses related to long-term outcomes. Finally, this study focused solely on CEUS as an imaging modality combined with O-RADS. Future research should explore the diagnostic value of other imaging technologies, such as CT and MRI, in combination with O-RADS to identify the optimal diagnostic strategy for clinical use.

In conclusion, the combined use of O-RADS, CEUS, and CA125 can accurately identify the benign and malignant of ovary-adnexal lesions and provide a reliable clinical reference. This approach offers a robust diagnostic tool to improve patient prognosis and safeguard their health.

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Disclosure of conflict of interest

None.

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